Estimating Exposure and Dose to Characterize Health Risks: The Role of Human Tissue Monitoring in Exposure Assessment

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Exposure assessment is an integral part of health risk characterization. Exposure assessments typically address three critical aspects of exposure: the number of people exposed to the environmental toxicant, at specific concentrations, for the time period of interest; the resulting dose; and the relative contribution of important sources and pathways to exposure/dose. Because historically both "point-of-contact" measurements and information about dose and related pharmacokinetic processes have been lacking, exposure assessments have had to rely on construction of "scenarios" to estimate exposure and dose. This could change, however, as advances in development of biologic markers of exposure and dose make it possible to measure and interpret toxicant concentrations in accessible human tissues. The increasing availability of "biomarkers," coupled with improvements in pharmacokinetic understanding, present opportunities to estimate ("reconstruct") exposure from measurements of dose and knowledge of intake and uptake parameters. Human tissue monitoring, however, is not a substitute for more traditional methods of measuring exposure, but rather a complementary approach. A combination of exposure measurements and dose measurements provides the most credible scientific basis for exposure assessment. — Environ Health Perspect (Suppl 3):13–30 (1995)

Key words: exposure assessment, tissue monitoring, environmental health risks, human exposure, exposure-dose relationships, risk assessment

Introduction

People are exposed to a variety of environmental agents, including biologic, chemical, and physical entities, in the air they breathe, the water they drink, the food they eat, the surfaces they contact, and the products they use. Sometimes, exposures to environmental toxicants are sufficient to cause adverse health consequences, such as birth defects, cancer, neurobehavioral effects, and respiratory disease. The quantitative estimation of such health risks, based on information about exposure and dose–response relationships, is fundamental to policy decisions about which risks are unacceptable and how best to manage them (*1–5*).

Establishing a causal relationship between exposures and subsequent disease or injury is usually difficult unless the link is very strong, as with radon-induced lung cancer in uranium miners. The difficulties arise because environmentally induced chronic disease is highly complex: multiple exposures and causative agents, long latency periods, and variability within and among individuals must be considered. The lack of appropriate data on human exposures, doses, and related effects contribute further to the difficulties encountered by risk assessors. In general, attempts to quantify health risks resulting from exposures to environmental agents are hindered by one or both of two pervasive problems: 1) appropriate and adequate scientific data are not available; and 2) available data are difficult or impossible to interpret because we do not have adequate scientific understanding (*6*).

Realistic risk assessment depends on accurate estimation of both exposures and toxicity related to health effects. Most of the research emphasis historically has been on reducing uncertainties associated with health effects (e.g., inherent toxicity, dose–response relationship). Experience has shown, however, that lack of exposure data and a defiency of understanding about important exposure mechanisms are major sources of scientific uncertainty in most risk assessments (*2–5,7–14*).

Human exposure analysis is currently recognized as an important topic of scientific investigation, one that is complementary to more traditional public health disciplines, such as epidemiology and toxicology. The need for exposure-related research is brought home by the paucity of empirical information available to estimate exposures, and associated doses, for most environmental agents deemed to have public health significance. The data on hand tend to be anectodal, fragmented, uneven, and narrowly focused on single pathways and routes of exposure for individual chemicals (*2–5,10,11,15–20*).

The purpose of this article is to explain how exposure assessments are conducted in the context of risk characterization, with particular emphasis on the importance of establishing the link between exposure and associated dose. We begin with a brief overview of the major uses of exposure information. We next focus specifically on the importance of exposure evaluation for realistic assessment of environmental health risks, and look conceptually at how individuals and groups who are potentially at greater risk are identified. We summarize the key concepts and definitions germane to exposure estimation, examine the basic components of exposure assessment, and compare three approaches to quantitative exposure estimation. The final section provides a short discussion of the growing importance of human tissue monitoring

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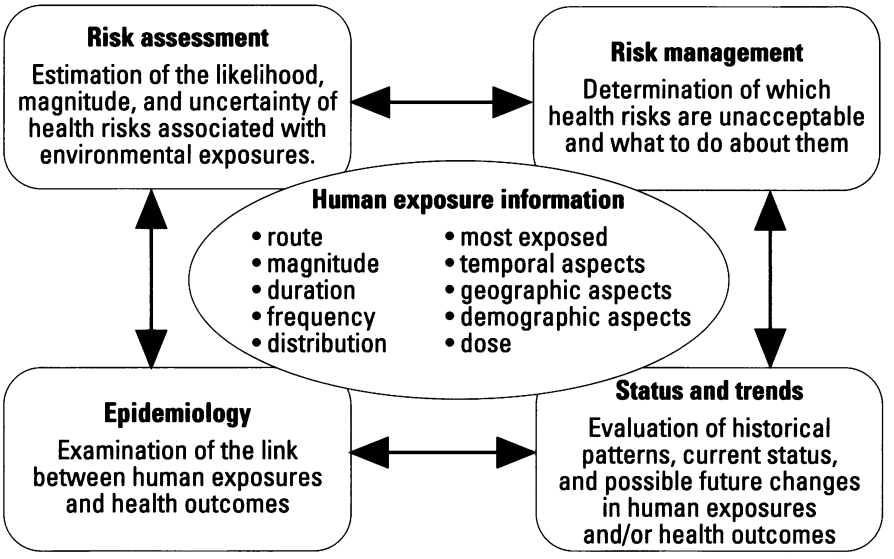

Figure 1. Important uses of human exposure information in the assessment and management of environmental health risks (*11*).

for realistic assessment of exposures to environmental agents.

Uses of Human Exposure Information

There are four interrelated uses of human exposure data for evaluation and protection of environmental health: risk assessment, risk management, status and trends analysis, and epidemiology (Figure 1).

Risk assessment is a formalized process for estimating the magnitude, likelihood, and uncertainty of environmentally induced health effects. Exposure assessment (e.g., exposure concentrations and related dose for specific pathways) and effects assessment (i.e., hazard identification, dose–response evaluation) are integral parts of this process. The goal is to use the best available information and knowledge to estimate health risks for the subject population, important subgroups within the population (e.g., children, pregnant women, and the elderly), and individuals at the center and "high end" of the exposure distribution (*1,10,11,21*).

The results of risk assessment feed directly into the risk management process carried out by policymakers. Risk management decisions are of four basic types: priority setting, determination of unacceptable risks, selection of the most cost-effective method to prevent or reduce unacceptable risks, and evaluation of the success of risk mitigation efforts. Exposure information is crucial to each of these decisions. In addition to data on exposures and related health effects, decisionmakers also must take account of the economic, engineering, legal, social, and political aspects of the problem (*11,15*).

Evaluation of current status and historical trends for exposures and doses is an important component of both risk assessment and risk management. It requires collecting exposure data over a relatively long period (e.g., 5 to 10 years), which assures that temporal trends can be identified and understood. Data on status and trends can be invaluable for identifying new or emerging problems, recognizing the relative importance of emission sources and exposure pathways, assessing the effectiveness of pollution controls, distinguishing opportunities for epidemiologic research, and predicting future changes in exposures and effects (*11,16*).

Epidemiology is the study of the determinants and distribution of health status (or health-related events) in human populations. Environmental epidemiology examines associations between exposures to environmental agents and associated disease or injury. It is a scientific tool that can sometimes detect environmentally induced health effects in populations, and it may offer opportunities to link actual exposures with adverse health outcomes (*11,17*)

Well-designed epidemiologic studies can provide unique and powerful information that is directly relevant to risk assessment and to risk management decisions. In addition to their other uses, these studies can characterize the health status of populations, describe disease occurrence through identification of explanatory factors, and evaluate efforts at disease prevention and reduction.

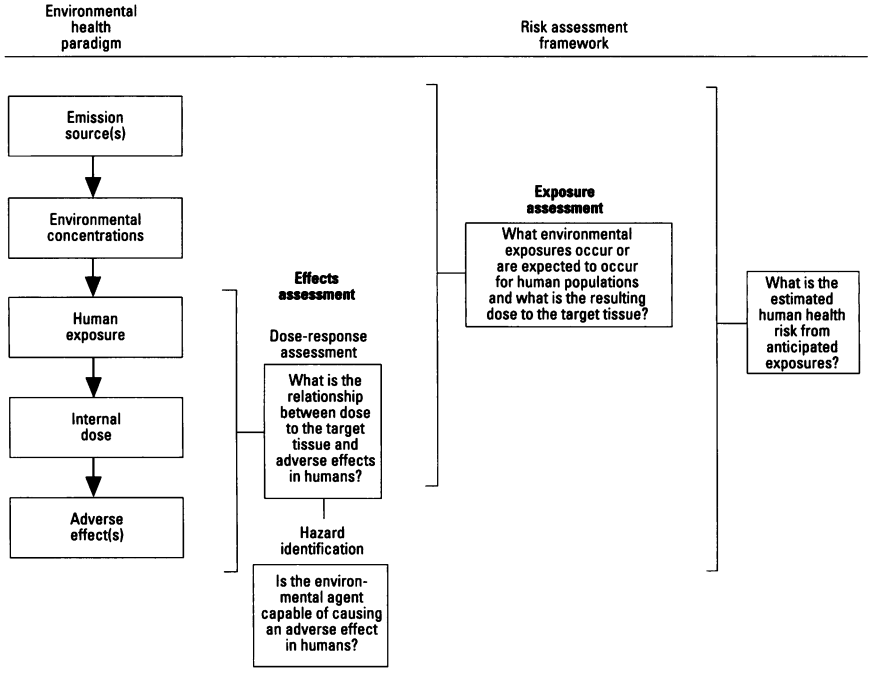

Figure 2. Relationship between an environmental health paradigm and the risk assessment framework. From Sexton et al. (*6*).

But without reliable exposure information, epidemiologic studies are much less useful for decision making. The excess risk for most environmentally related health effects is small, with relative risks and odds ratios typically less than 2. Failure to correctly classify or quantify exposures can introduce misclassification error that may artificially reduce the level of risk observed and thus limit the usefulness of the study (*11,17*).

In addition to these four uses of human exposure information, such data also may be essential for recognizing, diagnosing, and treating environmentally induced illness, such as lead poisoning. Although exposure assessments are undertaken for a variety of reasons, the subsequent discussion focuses on their use for characterizing environmental health risks.

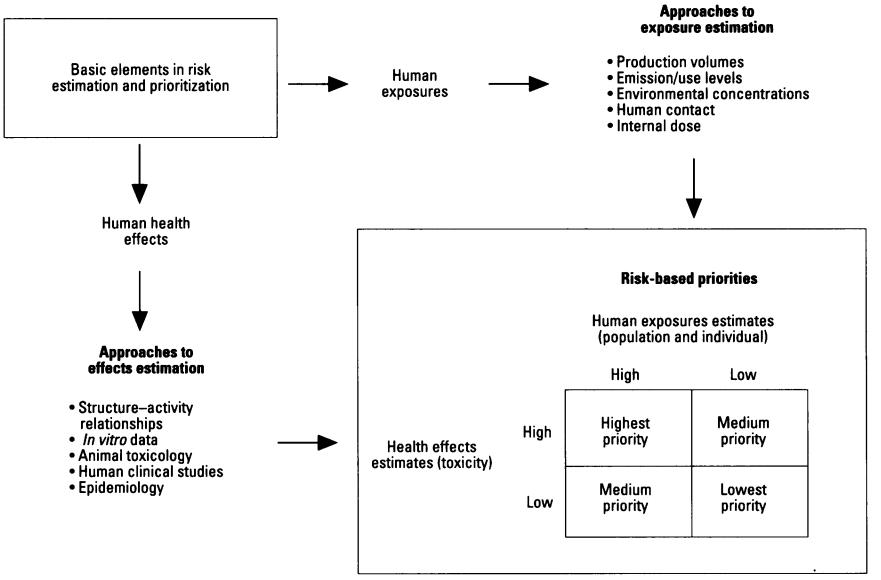

Figure 3. Basic elements in the estimation and prioritization of environmental health risks (*24*).

Exposure Assessment as a Critical Factor in Risk Characterization

Actions taken by society to protect its members from the harmful consequences of environmental agents are predicated on established or postulated links among emission sources, human exposures, and adverse health effects. The chain of events depicted in Figure 2 is an "environmental health paradigm": a simplified representation of the key steps between emission of toxic agents into the environment and potential disease or dysfunction in humans. This sequential series of events serves as a useful construct to aid in understanding and evaluating environmental health risks (*6,11,22*).

Estimation of health risks associated with environmental agents is composed of two primary activities: exposure assessment and effects assessment (Figure 2). Exposure assessment focuses on the initial portion of the environmental health paradigm: from sources, to environmental concentrations, to exposure, to dose. The major goal is to develop a qualitative and quantitative description of the environmental agent's contact with (exposure) and entry into (dose) the human body. Much emphasis is placed on estimating the magnitude, duration, and frequency of exposures, as well as estimating the number of people exposed to various concentrations of the agent in question. Ideally, the relative contribution of all important sources and pathways is determined at the same time (*1–5,21,23*).

Effects assessment (Figure 2) examines the latter portion of the events continuum: from exposure, to dose, to adverse health effects. The goals are to determine the intrinsic hazards associated with the agent (hazard identification) and to quantify the relationship between dose to the target tissue and related harmful outcomes (dose–response assessment). The overlap between exposure assessment and effects assessment reflects the importance of the exposure–dose relationship to both activities (*11*).

Risk characterization is the last phase of the risk assessment process. The results of the exposure and the effects assessments are combined to estimate the human health risks from the anticipated exposures. For example, a typical cancer risk characterization would estimate both the magnitude (e.g., 20 excess cancer cases yearly in the United States population) and the likelihood (e.g., maximally exposed person in the population runs a risk of 1 in 1,000,000 for developing cancer) of risks from exposures to an environmental carcinogen.

Conceptually, as shown in Figure 3, estimating and prioritizating health risks are deceptively simple. Risk is a combination of effects estimates and exposure estimates, where "highest" priority risks can be thought of as those that entail both "high" toxicity for the agent of interest (adverse effects are likely to occur in humans at relatively low exposures or doses), and "high" exposures for the population, subpopulation, or individuals of interest (exposures or doses are above a health-based standard). Conversely, "lowest" priority risks involve both "low" toxicity and "low" exposures. "Medium" priority risks are those for which either toxicity or exposure is "low" while the other is "high" (*24*).

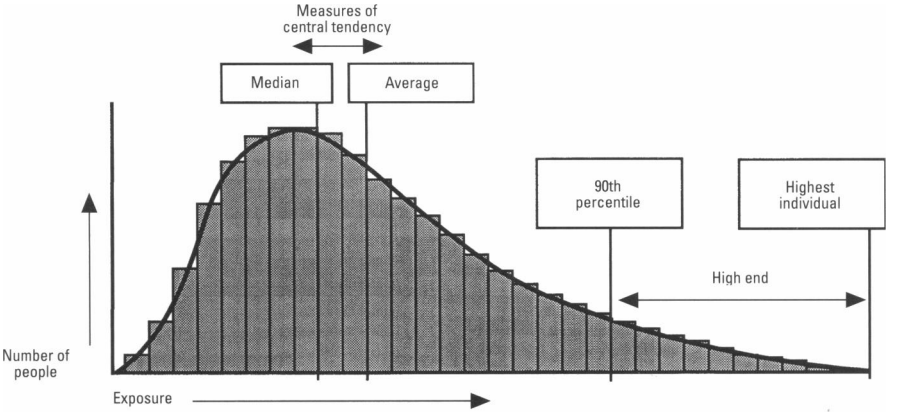

Figure 4. Common descriptors for human exposures to environmental agents. From Sexton et al. (*6*).

In practice, a variety of methods and approaches can be used to estimate both toxicity and exposure (Figure 3). Estimates are more realistic the closer the surrogate is to the event of interest (e.g., exposure), and the more accurate the model is for extrapolating to individuals for whom measurements are unavailable (*5,11*).

Identification and Description of Those Potentially at Greater Risk

An important goal of risk assessment is to identify and evaluate those populations, subpopulations, and individuals at potentially greater risk so that, if warranted, appropriate mitigation actions can be implemented. Conceptually, individuals and groups are deemed to be at potentially higher risk because they are exposed above a health-related benchmark, or more susceptible to the effects of exposures (*6,21,25*).

Measures of central tendency, such as the median and average, along with expressions of variability, like the standard deviation, are commonly used to describe the distribution of exposures for a population (Figure 4). Often, the relative position of an individual or group in the exposure distribution is of primary interest to the exposure assessor. Among the most frequently used descriptors for individual and subgroup exposures are values near the middle of the distribution; values above the 90th percentile, which is defined by the U.S. EPA as the "high end" of the distribution; and values at the extreme upper end, such as for the most exposed person in the population (*21*).

Systemic (noncancer) toxicants are usually assumed to have thresholds below which no effects occur. Accordingly, benchmarks to protect public health, such as reference concentrations and doses, ambient concentration standards, and workplace personal exposure limits, are often established at or below threshold levels. Exposures that exceed these values, whether they are above or below the 90th percentile, raise concerns about potentially elevated health risks (Figure 5A). In most cases, however, the shape of the dose–response curve above the benchmark is poorly defined, making it difficult or impossible to estimate risks quantitatively (*6,26–29*).

Quantitative risk assessment for carcinogens is a well-established (*30,31*) albeit controversial procedure. As part of the guidelines developed by the U.S. EPA, it is common practice to extrapolate from high to low dose by assuming a linear, nonthreshold model for carcinogenicity. Under this assumption, cancer risk for individuals can be estimated directly from the exposure or dose distribution, and the number of excess cancer cases (i.e., the increase above background rates) in the exposed population can usually be estimated by multiplying the average dose by both the total number of people exposed and the dose–response slope factor (Figure 5B). Although individual risk is assumed to increase with increasing exposure and dose all along the distribution, exposures of concern are typically defined to be those above some *de minimis* level of risk (e.g., a 1 in 1,000,000 excess risk of developing cancer).

Individuals and groups can also be at increased risk because they are more susceptible to the adverse effects of a given exposure. Among the potential causes of enhanced susceptibility are: inherent genetic variability, age, gender, preexisting disease (e.g., diabetes, asthma), inadequate diet, lifestyle factors (e.g., smoking), stress, and inadequate access to health care. To the extent feasible, it is important to identify these susceptible individuals and groups so that we can understand their exposures and take account of this information in assessing and managing risks (*1,21*).

Full characterization of health risks for a particular environmental agent requires

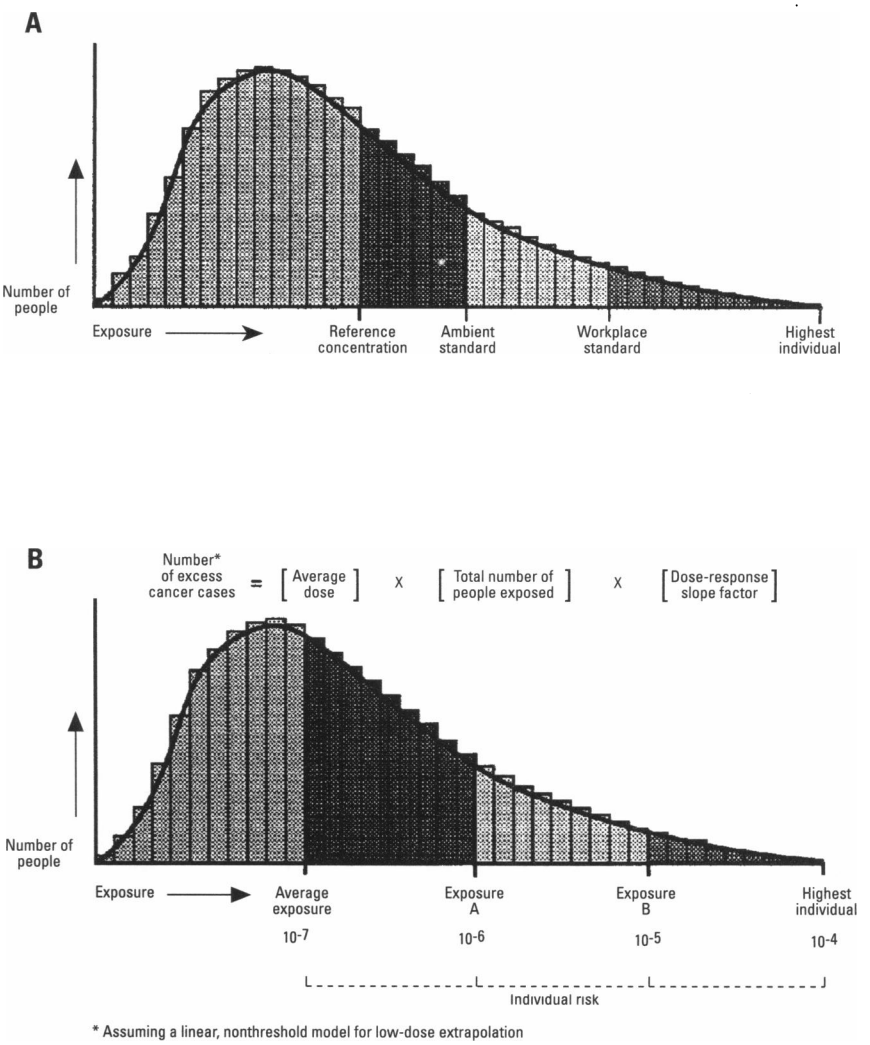

Figure 5. Human exposure distributions for (*A*) a hypothetical systemic (noncancer) toxicant and (*B*) a hypothetical carcinogen (*6*).

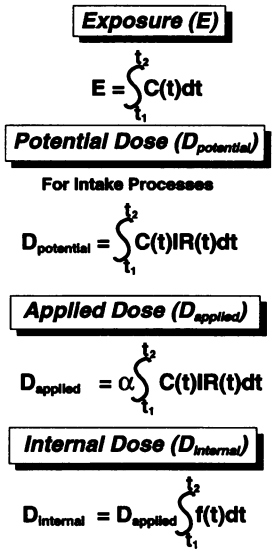

Figure 6. Mathematical expressions for some important exposure-related and dose-related events. *E*, magnitude of exposure; t_2–t_1, exposure duration; α, availability factor; C(t), exposure concentration as a function of time; IR, ingestion or inhalation rate; f(t), nonlinear absorption function. From U.S. EPA (*21*).

consideration and description of a number of factors, which fall into three major categories:

- population risk descriptors, including
  - number of "cases" over a specified time,
  - number (percentage) within specified range of a health-related benchmark (e.g., reference dose, reference concentration, National Ambient Air Quality Standard);
- subgroup risk descriptors, including
  - risks to more exposed subgroups,
  - risks to more susceptible subgroups; and
- individual risk descriptors, including
  - risks for individuals at the upper tail (e.g., 90th percentile and above) of the exposure distribution,
  - risks for individuals near the center (e.g., mean, median) of the exposure distribution, and
  - risks for the most exposed person in the population (*21,23,25*).

In specific assessment situations, different descriptors may be more or less appropriate, depending on the ultimate uses of the information and the quality and quantity of available data.

From the preceding discussion, the importance of exposure and dose assessment for identifying and evaluating those who may be at higher-than-average risk should be obvious. Realistic estimates of exposure and dose are also essential to informed decisions about whether these risks are unacceptable, and, if so, what to do about them. Furthermore, exposure and dose information is a critical component of efforts to establish whether control strategies that have been implemented were successful in preventing or reducing risks. It is easy to see, then, why exposure and dose assessment, in combination with effects assessment, form the scientific foundation for credible characterization, comparison, management, and communication of environmental health risks.

Exposure to Environmental Agents: Concepts and Definitions

So far, we have been using the terms "exposure" and "dose" without explicitly defining them. Although they are well-established concepts familiar to all environmental health scientists, their meaning often varies depending on the context of the discussion. It is important, however, that these and related terms be defined precisely. In the following section we describe and define important exposure-related terms used in this article to be consistent with the U.S. EPA's Exposure Assessment Guidelines (*21*).

Exposure and Exposure Concentration

Exposure is defined as contact of a biologic, chemical, or physical agent with the outer part of the human body, such as the skin, mouth, or nostrils. Although there are many instances where contact occurs with an undiluted chemical (e.g., use of degreasing chemicals for cleaning hands), contact more often occurs with a carrier medium—air, water, food, dust, or soil—that contains dilute amounts of the agent. "Exposure concentration" (e.g., mg/l, mg/kg, $\mu g/m^3$/hr) is defined as the concentration of an environmental agent in the carrier medium at the point of contact with the body.

Exposure Estimation by Integration and Summation

A minimal description of exposure for a particular route must include at least two related attributes: concentration of the agent in the carrier medium (exposure concentration); and time of contact (duration). If the exposure concentration is integrated over the duration of contact (Figure 6), the area under the resulting curve is the magnitude of the exposure in units of concentration times time (e.g., mg/l/day, mg/kg/day, $\mu g/m^3$/hr). This is the method of choice to describe and estimate short-term exposures, where integration times are on the order of minutes, hours, or days.

Over periods of months, years, or decades, exposures to most environmental agents occur intermittently rather than continuously. Yet long-term health effects, such as cancer, are customarily evaluated

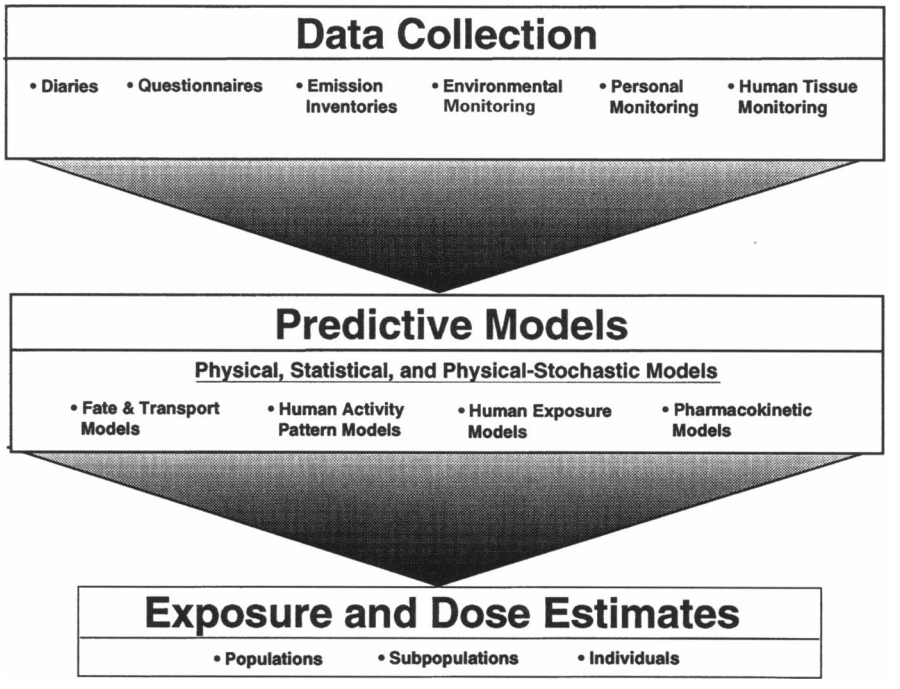

Figure 7. The relationship among data collection, predictive models, and exposure and dose estimates.

based on an average dose over the period of interest (typically years), rather than as a series of intermittent exposures. Consequently, long-term doses are usually estimated by summing doses across discrete exposure episodes and then calculating an average dose for the period of interest (e.g., year, lifetime). Although the integration approach can also be used to estimate long-term exposures or doses, its application to time periods longer than about a week is usually difficult and inconvenient.

Exposure Measurements and Models

Direct measurements are the only way to establish unequivocally whether and to what extent individuals are exposed to specific environmental agents. But it is neither affordable nor technically feasible to measure exposures for everyone in all populations of interest. Models, which are mathematical abstractions of physical reality, may obviate the need for such extensive monitoring programs by providing estimates of population exposures (and doses) that are based on a smaller number of representative measurements (Figure 7). The challenge is to develop appropriate and robust models that allow for extrapolation from relatively few measurements to estimates of exposures and doses for a much larger population (*2–5,21*).

For relatively small groups, measurements or estimates can be made for some or all of the individuals separately, and then combined as necessary to estimate the exposure (or dose) distribution. For larger groups, exposure models and statistics can sometimes be used to derive an estimate of the distribution of population exposures, depending on the quantity and quality of existing data. Monte Carlo and other statistical techniques are increasingly being used to generate and analyze exposure distributions for large groups (*21,32*).

Exposure in the Context of an Environmental Health Paradigm

An expanded and more detailed version of the environmental health paradigm presented in Figure 2 is depicted in Figure 8. It shows the domain of exposure assessment, which includes important events, mechanisms, and processes that provide a context for understanding and estimating exposures and doses for environmental agents.

The release of an agent into the environment, its ensuing transport, transformation, and fate in various environmental media, and its ultimate contact with people are critical events in understanding

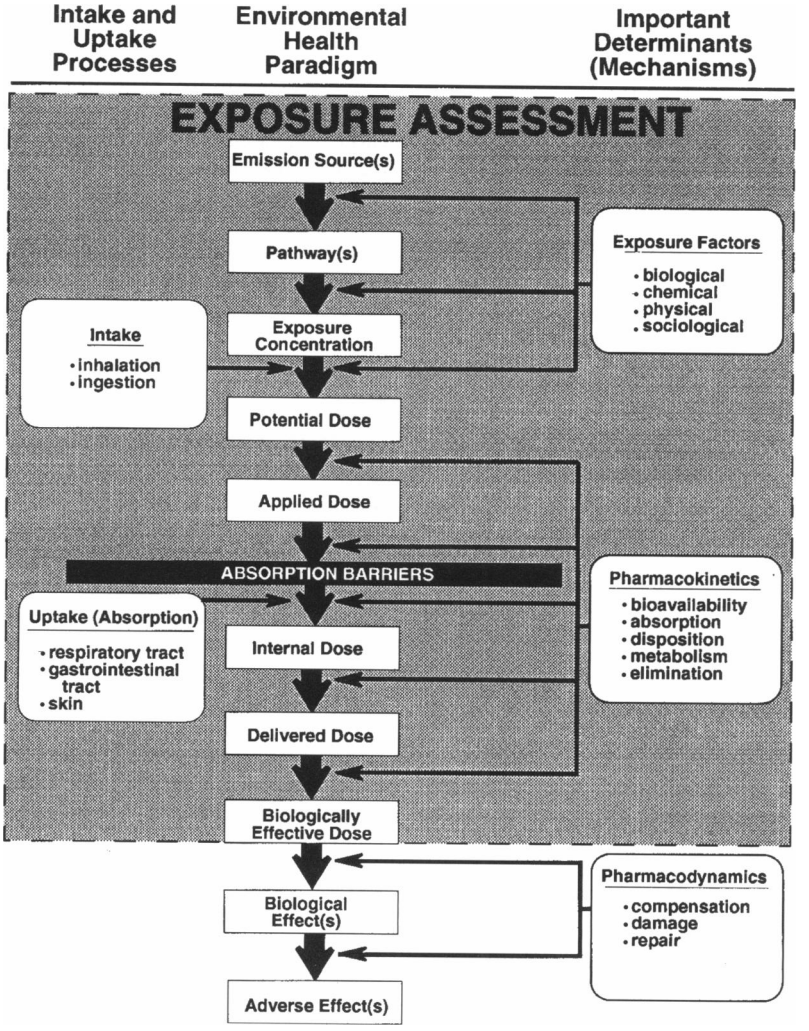

Figure 8. The domain of exposure assessment in relation to an environmental health paradigm.

how and why exposures occur. Definitions for key events in the continuum are summarized below (*21*).

Emission Source. The point or area of origin for an environmental agent is known as a "source." Agents are released into the environment from a wide variety of sources, which are often categorized as point sources (e.g., incinerator) versus area sources (e.g., urban runoff), stationary sources (e.g., refinery) versus mobile sources (e.g., automobile), and anthropogenic sources (e.g., landfill) versus nonanthropogenic sources (e.g., natural vegetation).

Exposure Pathway. An exposure pathway is the physical course taken by an agent as it moves from a source to a point of contact with a person.

Exposure Concentration. Exposure concentration is the concentration of an agent in a carrier medium at the point of contact with the outer boundary of the human body.

Most exposure assessments do not stop at exposure concentration, since that information alone is not very useful unless it is converted to dose or risk. Assessments therefore usually estimate how much of an agent is expected to enter the body. This transfer of an environmental agent from the exterior to the interior of the body can occur by either or both of two basic processes: intake and uptake.

Intake. Intake is associated with ingestion and inhalation. The agent, which is likely to be part of a carrier medium (e.g., air, water, food), enters the body by bulk transport, usually through the nose or mouth. The rates of bulk transport into the body are assumed to be the same for both the agent and the carrier medium. The amount of the agent that crosses the boundary per unit time can be referred to

as the "intake rate," which is the product of the exposure concentration times the rate of either ingestion or inhalation.

Uptake. Uptake is associated with the dermal route of exposure, as well as with ingestion and inhalation after intake has occurred. The agent, as with intake, is likely to be part of a carrier medium (e.g., water, soil, consumer product), but enters the body by crossing an absorption barrier, such as the skin, respiratory tract, or gastrointestinal tract. The rates of bulk transport across the absorption barriers are generally not the same for the agent and the carrier medium. The amount of the agent that crosses the barrier per unit time can be referred to as the "uptake rate". This rate is a function of the exposure concentration, as well as of the permeability and surface area of the exposed barrier. The uptake rate is also called a "flux".

Dose. Once the agent enters the body by either intake or uptake, it is described as a "dose." Several different types of dose are relevant to exposure estimation.

Potential (Administered) Dose. Potential, or administered dose, is the amount of the agent that is actually ingested, inhaled, or applied to the skin. The concept of potential dose is straightforward for inhalation and ingestion, where it is analogous to the dose administered in a dose–response experiment. For the dermal route, however, it is important to keep in mind that potential (or administered) dose refers to the amount of the agent, whether in pure form or as part of a carrier medium, that is applied to the surface of the skin. In cases where the agent is in diluted form as part of a carrier medium, not all of the potential dose will actually be touching the skin.

Applied Dose. Applied dose is the amount of the agent directly in contact with the body's absorption barriers, such as the skin, respiratory tract, and gastrointestinal tract, and therefore available for absorption. Information is rarely available on applied dose, so it is calculated from potential dose based on factors such as bioavailability (Figure 6).

Internal (Absorbed) Dose. The amount of the agent absorbed, and therefore available to undergo metabolism, transport, storage, or elimination, is referred to as the "internal" or "absorbed dose" (Figure 6).

Delivered Dose (Body Burden). The portion of the internal (absorbed) dose that reaches a tissue of interest is called the "delivered dose."

Biologically Effective (Target) Dose. The portion of the delivered dose that reaches the site or sites of toxic action is called the "biologically effective dose."

The link, if any, between biologically effective dose and subsequent disease or illness depends on the relationship between dose and response (e.g., shape of the dose–response curve), underlying pharmacodynamic mechanisms (e.g., compensation, damage, repair), and important susceptibility factors (e.g., health status, nutrition, stress, genetic predisposition).

Biologic Effect. A measurable response to dose in a molecule, cell, or tissue is termed a "biologic effect." The significance of a biologic effect, whether it is an indicator or a precursor for subsequent adverse health effects, may not be known.

Adverse Effect. A biologic effect that causes dysfunction, injury, illness, or death is defined as an "adverse health effect."

Linking Exposure Events and Dose Events

The schematic framework in Figure 9 shows how the interrelationships among significant exposure- and dose-related events in the paradigm can be conceived. The example assumes that perfect information on exposure and dose is available for a hypothetical population exposed to a single agent by multiple pathways and routes.

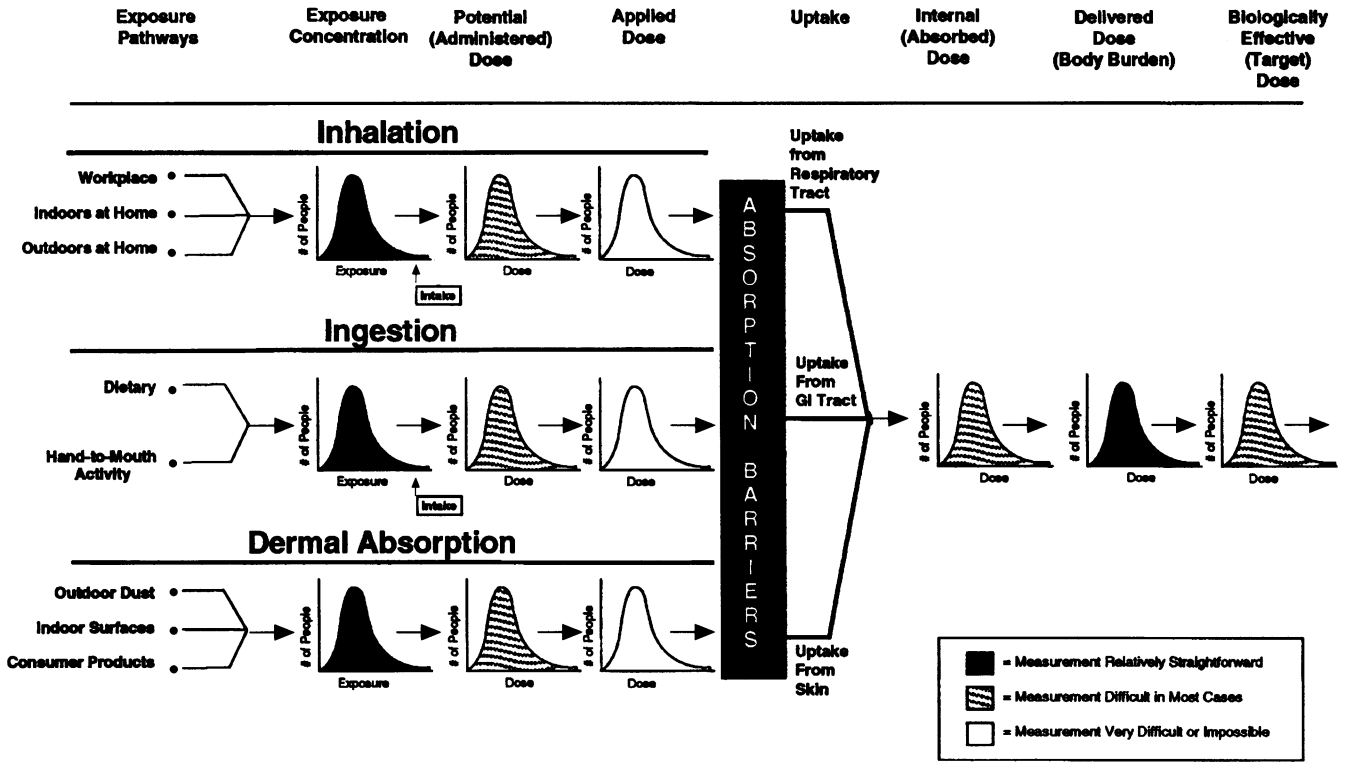

Figure 9. The relationship among important exposure-related and dose-related events in the context of exposure assessment.

It illustrates the route-specific nature of both exposure and dose for the environmental agent prior to its absorption into the body (uptake), and the integration of it across all routes that occurs subsequent to uptake.

It is important to keep in mind that, although events along the continuum are correlated, the relative position of a particular individual within a distribution may change dramatically from one event to the next. It is not the case, for example, that the person with the highest (or lowest) exposure will necessarily have the highest (or lowest) dose, and vice versa. Moreover, the distribution itself may be altered (e.g., an increase or decrease in variance) as the agent or its metabolite/derivative moves through the various stages from exposure concentration to biologically effective dose.

To make realistic estimates for a specific event (e.g., an internal dose), it is necessary to have at least one of two types of information: measurements of the event itself (e.g., internal dose); or measurements of an earlier (e.g., potential dose) or later (e.g., delivered dose) event in the continuum. It is also necessary to understand the critical intervening mechanisms and processes (e.g., pharmacokinetics) that govern the relationship between the event measured and the event of interest (e.g., internal dose). Unless such data are on hand, extrapolating from one event to another, moving from either exposure to dose (from left to right in Figure 9) or from dose to exposure (from right to left in Figure 9), is problematic.

Suitable data and adequate understanding are seldom, if ever, available to describe and estimate all of the significant events for the groups and individuals of interest. Generally speaking, measurement of exposure concentration and delivered dose (body burden) is relatively straightforward, while measurement of potential (administered) dose and internal (absorbed) dose is usually possible only with substantially greater effort. Measurement of biologically effective (target) dose is also possible in some cases. However, it is typically difficult or impossible, given existing approaches and methods, to measure applied dose.

This situation presents us with a conundrum. We would like to have realistic estimates of exposure concentrations of an agent for all important pathways, and the resulting biologically effective dose. Typically, however, if relevant data are available at all, they are related to exposure concentrations for one pathway or route of exposure. In the few cases where data on dose are also available, these data usually reflect delivered dose (body burden) rather than biologically effective dose. Even if suitable measurements of both exposure concentration and delivered or target dose are on hand, the absence of pharmacokinetic understanding to relate these measurements to each other, as well as to other significant events along the continuum, seriously impairs efforts to establish the link between exposure and dose.

We are thus left with a situation in which we can measure specific events on either side of the body's absorption boundaries; but we can relate them to each other only by using a series of unsubstantiated, even heroic, assumptions. Yet it is precisely this relationship between exposure and dose that is critical to realistic risk characterization.

Basics of Exposure Assessment

Assessing human exposure to an environmental agent involves the qualitative description and the quantitative estimation of the agent's contact with (exposure) and entry into (dose) the body. Although no two exposure assessments are exactly the same, most assessments address three key areas that are important for risk assessment and for risk management decisions: the number of people exposed at specific concentrations for the time period of interest; the resulting dose; and the contribution of important sources and pathways to exposure or dose. A list of the types of estimates that might comprise a comprehensive exposure assessment might include the following (*21,33*):

Exposure
- routes and durations of interest;
- distribution (e.g., mean, variance, 90th percentile)—population, important subpopulations (e.g., more exposed, more susceptible);
- individuals—average, upper tail of distribution, most exposed in population;

Dose
- link with exposure;
- distribution (e.g., mean, variance, 90th percentile)—population, important subpopulations (e.g., higher doses, more susceptible);
- individuals—average, upper tail of distribution, highest dose in population;

Causes
- relative contribution of important sources;
- relative contribution of important environmental media;
- relative contribution of important exposure pathways;
- relative contribution of important routes of exposure;

Variability
- within individuals (e.g., changes in exposure from day-to-day for the same person);
- between individuals (e.g., differences in exposure on the same day for two different people);
- between groups (e.g., different socioeconomic classes or residential locations);
- over time (e.g., changes in exposure/dose from one year to the next);
- across space (e.g., changes in exposure/dose from one region of the country to another)

Uncertainty
- lack of data—statistical error in measurements, model parameters, etc.; misidentification of hazards and causal pathways;
- lack of understanding—mistakes in functional form of models, misuse of proxy data from analogous contexts.

The first step in any exposure assessment must be to determine which data are necessary; the next step must be to specify how to obtain them. These steps can be accomplished by addressing a series of questions about the assessment's purpose, scope, level of detail, and approach (*21,23*).

Purpose

Will the assessment:
- support regulations for specific emission sources?
- set standards for specific environmental media?
- determine the need to remediate a waste site or chemical spill?
- enable us to set priorities?
- determine whether an agent should be introduced into commerce?

Scope
- Which agent or mixture of agents will be evaluated?
- Will the assessment be site-specific, local, regional, or national?
- Which sources, pathways, media, routes, and populations are important?

Level of Detail
- What level of detail and degree of confidence are adequate to achieve the purpose of the assessment?
- Will resource limitations limit the depth, breadth, and utility of the effort?
- What level of detail is needed about linkages among sources, exposures, doses, effects and risks?

Approach

- Is measuring exposures, constructing a scenario, or reconstructing internal dose the most appropriate way to estimate exposures?
- What measurements, methods, and/or models are available to provide the needed information?
- How will critical data needs and gaps in knowledge be addressed?

Answers to these questions provide a context, at the outset, for identifying viable options and then for deciding how best to conduct the necessary exposure assessment.

Three Approaches to Quantitative Exposure Assessment

Quantitative estimation of exposure is often the central feature of assessment activities. The quantitative estimation of exposure can be approached in three general ways: point-of-contact measurements, construction of a scenario, and reconstruction of internal dose to calculate associated exposures (*21,23*).

Point-of-contact Measurements. Measurement of actual exposure as it occurs (i.e., exposure concentration and duration) at the point of contact with the human body.

Scenario Evaluation. Estimation of exposure by use of a hypothetical but plausible scenario to analyze exposure concentration and time of contact.

Exposure Reconstruction. Estimation of exposure from dose, based on reconstruction of internal dose from human tissue measurements and knowledge of pharmacokinetics, and data or assumptions about intake and uptake rates.

These three generic approaches to quantitative estimation of exposure are independent and complementary. Each relies on different kinds of data and has different strengths and weaknesses. It is potentially useful, therefore, to employ multiple approaches as a way of checking the robustness of results. Among other factors, the choice of which method to use will depend on the purpose of the assessment and the availability of suitable methods, measurements, and models (*21*).

Point-of-contact Measurement

Point-of-contact measurements quantify exposure as it occurs by measuring the concentration of the agent at the interface between the person and the environmental (carrier) medium. Radiation dosimeters, such as those worn on the lapel of laboratory technicians, are perhaps the best-known example. These small badges measure radiation exposure as it occurs, providing an integrated measurement over a specified period. Other examples include small, personal monitors for carbon monoxide, particles, and volatile organic chemicals such as those used in EPA's Total Exposure Assessment Methodology (TEAM) studies (*14,21,34*). Examples of point-of-contact measurements and their relevance to exposure assessment are provided in Table 1.

The major strength of this approach is that it measures exposure directly for the monitoring period. Typically, however, this period is relatively short (e.g., minutes, hours, days), thereby limiting the usefulness of this approach for estimating lifetime exposure. Furthermore, point-of-contact measurements are costly and time consuming, can be burdensome for the participants, and are often constrained by a lack of suitable methods (*14,21,34*).

Table 1. Examples of "point-of-contact" measurements used in exposure assessments.[a]

Type of measurement	Element estimated	Examples	Typical information needed to characterize exposure
Air pump/particulates and vapors	Exposure of an individual or population via the air	TEAM study	All of these methods directly measure individual exposure during time sampled. To characterize exposure to population, relationships between individuals and the population must be established as well as relationships between times sampled and other times for the same individuals, and relationships between sampled individuals and other populations. To make these links, activities of the sampled individuals compared to populations characterized should be described in some detail.
Passive vapor sampling	Exposure of an individual or population via the air medium	TEAM study	
Split sample of food and drinking water	Exposures of an individual or population via ingestion	TEAM study	
Skin patch samples	Dermal exposure of an individual or population	Pesticide applicator study	

TEAM, total exposure assessment methodology. [a]Taken from U.S. EPA guidelines (*21*).

Scenario Construction

When direct measurements are not available for the population of interest, a scenario approach is frequently used to estimate exposures and doses. The exposure assessor uses the available facts (e.g., databases, models), in combination with assumptions, inferences, and professional judgment, to construct a plausible set of assumptions (i.e., a scenario) that describes quantitatively how contact occurs between people and environmental agents.

A typical scenario estimates exposure by merging two separate but essential components of exposure: concentration of the agent in the environmental (carrier) medium, estimated by using data or making assumptions about source–pathway– exposure interactions; and contact time with people, estimated by using existing data and knowledge, or by making reasonable assumptions about time–activity patterns, lifestyle characteristics, residential proximity to sources, and other factors. The doses related to exposure are estimated using knowledge and assumptions about relevant pharmacokinetic processes. Examples of the types of measurements useful in constructing a scenario and their relevance to exposure assessments are provided in Table 2. Both the "microenvironmental" (*3,21,34*) and pathway–exposure factors ("PEF") methods for exposure estimation (*19*) are variations of the scenario approach.

The primary advantage of the scenario approach is that it enables assessors to make estimates of exposure and dose with very limited data. On the other hand, the uncertainty introduced by the need to make assumptions and inferences in the face of limited information is also its major disadvantage. The scenario approach is most useful when the assessor has some insight into the completeness, soundness, validity, and uncertainty associated with the underlying assumptions and inferences, and understands their overall effect on the uncertainty of the estimated values for exposure and/or dose (*21,23*).

Reconstructive Exposure Assessment

The third approach uses dose information to estimate exposure. If measurements (e.g., body burden, elimination levels) are available to "reconstruct" internal dose, past exposures can be calculated by incorporating information or assumptions about rates of intake and uptake. Appropriate

application of this approach depends on the availability of measurements of biomarkers in human tissue so that internal dose can be realistically reconstructed (calculated), and adequate information to accurately estimate intake, uptake, and metabolic rates. Examples of the types of biomarkers measured in human tissue that can be used for reconstructing internal dose and their relevance to exposure assessment are given in Table 3.

The strength of the reconstructive approach is that it can demonstrate unequivocally that exposure and uptake have occurred. However, because internal dose is integrated across all routes of exposure, the method does not usually provide information about the relative importance of inhalation, ingestion, and dermal absorption. Perhaps the most serious problem with implementing this approach is

Table 2. Examples of types of measurements useful in construction of scenarios for exposure assessments.[a]

Type of measurement	Element estimated	Examples	Typical information needed to characterize exposure
Fixed-location monitoring	Environmental medium; samples used to establish long-term indications of media quality and trends	National Stream Quality Accounting Network (NASQAN), water quality networks, air quality networks.	Population location and activities relative to monitoring locations; fate of pollutants over distance between monitoring and point of exposure; time variation of pollutant concentration at point of exposure
Short-term media monitoring	Environmental or ambient medium; samples used to establish a snapshot of quality of medium over relatively short time	Special studies of environmental media, indoor air	Population location and activities (this is critical since it must be closely matched to variations in concentrations due to short period of study); fate of pollutants between measurement point and point of exposure; time variation of pollutant concentration at point of exposure
Source emissions monitoring	Release rates to the environment from sources; often given in terms of relationships between release amounts and various operating parameters of the facilities	Stack sampling, effluent sampling, leachate sampling from landfills, incinerator ash sampling, fugitive emissions sampling, pollution control device sampling	Fate of pollutants from part of entry into the environment to point of exposure; population location and activities; time variation of release
Food samples	Concentrations of contaminants in food supply	U. S. Food and Drug Administration Total Diet Study, market basket studies, shelf studies, cooked-food sampling	Dietary habits of various age, sex, or cultural groups; relationship between food items sampled and groups (geographic, ethnic, demographic) studied; relationships between concentrations in uncooked versus prepared food
Drinking water samples	Concentrations of pollutants in drinking water supply	Ground Water Supply Survey, Community Water Supply Survey, tap water samples	Fate and distribution of pollutants from point of sample to point of sample to point of consumption; population served by specific facilities and consumption rates; for exposure due to other uses (e.g., cooking, showering), need to know activity patterns and volatilization rates
Consumer products samples	Concentration levels of the products	Shelf surveys, e.g., solvent concentration in household cleaners	Establish use patterns and market share of particular products, individual exposure at various usage levels, extent of passive exposure
Breathing zone measurements	Exposure to airborne chemicals	Industrial hygiene studies, occupational surveys, indoor air studies	Location, activities, and time spent relative to monitoring locations; protective measures/avoidance
Micro-environmental studies	Ambient medium in a defined area, e.g., kitchen, automobile interior, office setting, parking lot	Special studies of indoor air, house dust, contaminated surfaces, radon measurements, office building studies	Activities of study populations relative to monitoring locations and time exposed
Surface soil samples	Degree of contamination of soil available for contact	Soil samples at contaminated sites	Fate of pollution on or in soil; activities of potentially exposed populations
Soil core	Soil including pollution available for groundwater contamination; can be an indication of quality and trends over time	Soil samples at hazardous waste sites	Fate of substance in soil; speciation and bioavailability, contact and ingestion rates as a function of activity patterns and age
Fish tissue samples	Extent of contamination of edible fish tissue	National Shellfish Survey	Relationship of samples to food supply of individuals or population of interest; consumption habits; preparation habits

[a]Taken from U. S. EPA guidleines (*21*).

Table 3. Examples of human tissue measurements used in exposure assessments.

Type of measurement	Element estimated	Examples	Typical information needed to characterize exposure
Breath	Total internal dose for individuals or population (usually indicative of relatively recent exposures)	Measurement of volatile organic chemicals (VOCs), alcohol. (usually limited to volatile compounds)	Relationship between individuals and population; exposure history (i.e., steady-state or not) pharmacokinetics (e.g., chemical half-life), possible storage reservoirs within the body; Relationship between breath content and body burden
Blood	Total internal dose for individuals or population (may be indicative of either relatively recent exposures to fat-soluble organics or long-term body burden for metals)	Lead studies, pesticides, heavy metals (usually best for soluble compounds, although blood lipid analysis may reveal lipophilic compounds)	Same as for breath, plus relationship between blood content and body burden
Adipose tissue	Total internal dose for individuals or population (usually indicative of past exposure in weeks to months range; can sometimes be used to evaluate exposure patterns)	National Human Adipose Tissue Survey—dioxin and PCB studies (usually limited to lipophilic compounds)	Same as for breath, plus relationship between adipose content and body burden
Nails, hair	Total internal dose for individuals or population (usually indicative of long-term averages for fat soluble organics)	Heavy metal studies (usually limited to metals)	Same as for breath, plus relationship between nails, hair content and body burden
Urine	Total internal dose for individuals or population (usually indicative of elimination rates); time from exposure to appearance in urine may vary, depending on chemical	Studies of tetrachloroethylene and trichloroethylene	Same as for breath, plus relationship between urine content and body burden

Taken from U.S. EPA guidelines (*21*).

the lack of physiologically based pharmacokinetic models for the environmental agents of interest. Without a good understanding of pharmacokinetics, including bioavailability, absorption, disposition, metabolism, and elimination, reconstructing internal dose and calculating previous exposures are highly uncertain (*21,23*).

Role of Human Tissue Monitoring in Exposure Assessment

The vast majority of quantitative risk assessments conducted by the U.S. EPA have dealt with lifetime cancer risks from long-term exposures to low levels of single chemicals via one pathway or route. In the face of a serious lack of data on both cancer potency and lifetime exposures in humans, an elaborate set of guidelines has been developed for cancer risk assessment (*30,31*). The guidelines provide assessors with formal guidance on how and when to apply a variety of "default" assumptions to estimate carcinogenic risk. For example, in the absence of evidence to the contrary, it is common to assume that a high dose of a carcinogen received over a short time is equivalent to a corresponding low dose spread over a lifetime.

Most cancer risk assessments have been done by constructing scenarios because there is an absence of adequate and appropriate data; because there is a lack of scientific understanding to interpret available data. Of necessity, these scenarios have incorporated default assumptions to estimate exposure and dose. The scenario approach is based on a logical, stepwise analysis of the important events in the environmental health paradigm (Figures 8,9), from source, through pathways, to exposure, and ultimately to biologically effective dose. Important parameters (e.g., emission rates, product-use patterns, transport and fate processes, concentrations in food and water, human consumption patterns, uptake rates, metabolism, excretion)

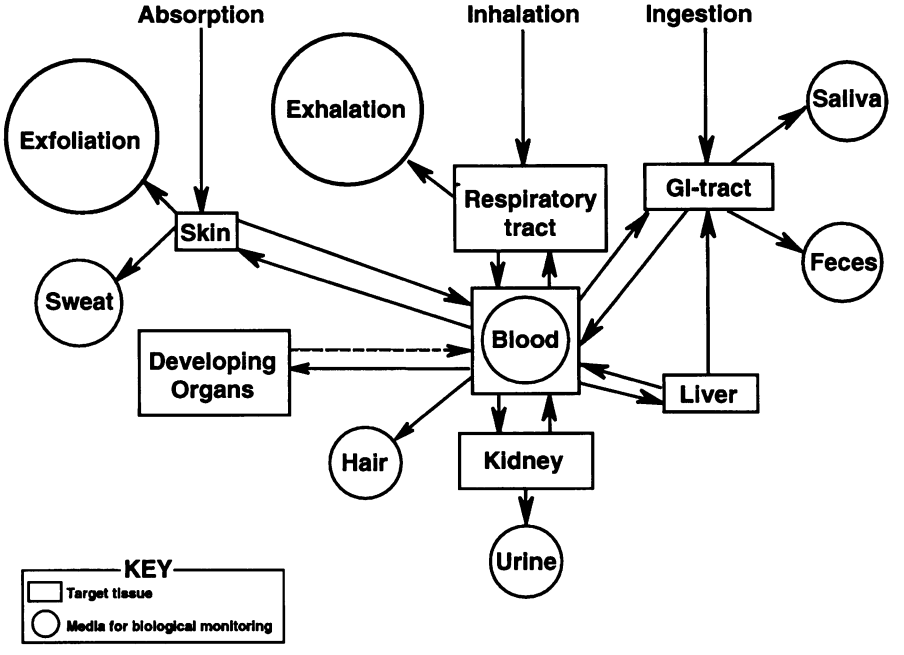

Figure 10. Simplified diagram of exposure routes, uptake sites, target tissue, and potential tissue and excreta for biological monitoring (*40*).

are either estimated from available data or assumed to be represented adequately by default values.

Because information is lacking, scenarios do not usually include a complete description of the exposure and dose distribution for the population of interest. Instead, scenarios emphasize estimating several points on the population distribution of lifetime individual exposures (or doses) (Figures 4,5B). Historically, three of these points have been: average exposure (dose), which is related to the total number of excess cancer cases expected in the population from the anticipated exposures; exposure (dose) for an individual in the upper tail of the distribution; and exposure (dose) for the most exposed individual in the distribution. Although scenarios have obvious limitations, such as lack of data, unvalidated default assumptions, and point estimates of exposure or dose, that contribute significantly to uncertainties in risk assessment, they remain the only viable method to estimate exposure or dose in the absence of direct measurements.

Historically, human tissue measurements have played a relatively small role in most exposure assessments because of the nature of the risks being assessed (e.g., lifetime cancer risk related to "average" lifetime exposure or dose), the types of questions being asked (e.g., what incremental risks are associated with a single source/pathway/route), the lack of appropriate human tissue data (e.g., no data for the population/situation of interest), and our still largely deficient understanding of pharmacokinetics (e.g., we cannot yet interpret human tissue measurements in terms of exposure).

Biologic Markers (Biomarkers) of Exposure

Many of the dose-related and health-related events in the environmental health paradigm (Figures 8,9) occur at inaccessible sites in the body (e.g., liver, developing organs). Biologic markers (biomarkers) are indicators of these significant but inaccessible events that can be measured in accessible human tissues (e.g., blood) (Figure 10). Biomarkers fall into several categories, including the following:

- Unchanged exogenous agents—solvents, asbestos fibers, PCBs, ethanol, nicotine, and heavy metals;
- Metabolized exogenous agents (precursors in parentheses)—phenol (benzene), DDE (DDT), cotinine (nicotine) BPDE, I (benzo[*a*]pyrene), retinol (β-carotene), acrolein (cyclophosphamide);
- Endogenously produced molecules (exposure/disease in parentheses)—exposure markers, e.g., acetyl cholinesterase (organic phosphate pesticides), γ-glutamyltransferase (liver toxins), porphyrin ratios (lead and other metals); and disease markers, e.g., alpha-fetoprotein (liver cancer), SGOT (myocardial infarction), and creatine kinase (muscle trauma);
- Molecular changes (exposure in parentheses)—glycosylated hemoglobin (dietary glucose), DNA adducts (chemical carcinogens), protein adducts (electrophilic chemicals), chromosome aberrations (clastogens), alkylated amino acids (electrophilic chemicals), and micronuclei (clastogens); and
- Cellular/tissue changes (in response to various toxins)—cell histology, lymphocyte ratios, sperm mobility, sperm counts, macrophage activity, and red blood cell counts

and they can be obtained from many human tissues and excreta by invasive and noninvasive methods. (Noninvasive means that sample collection does not require penetration of the body envelope. A complete definition of invasive/noninvasive must also include consideration of social, cultural, and pyschological factors.) Invasive methods may involve expired air, saliva, semen, urine, sputum, hair, feces, breast milk, or fingernails. Noninvasive methods may yield samples from blood, lung tissue, bone marrow, amniotic fluid, liver tissue, bone, follicular fluid, adipose tissue, or blood vessels. The expanding availability of biomarkers for events of interest in the environmental health paradigm (Tables 4,5) offers increasing potential to use them in exposure estimation (*2–5, 35–44*).

Table 4. Examples of biomarkers for significant events in the environmental health paradigm.[a]

Exposure biomarkers	Marker	Exposure	Biologic media
Delivered dose markers	Cotinine	Nicotine in cigarette smoke	Body fluids
	Lead	Lead in environment	Body fluids and tissues (hair, nails, teeth)
	DDE	DDT	Adipose tissue
	Aflatoxin	Aflatoxin in food stuff	Body fluids
	Mutagenesis	Chemical mutagens	Body fluids
Biological effective dose markers	DNA adducts	Benzo[*a*]pyrene	WBC
	Protein adducts (hemoglobin)	Ethylene oxide	RBC
Biologic effects (response) markers	**Chromosomal**		
	Aberrations	Mutagenic chemicals	WBC
	Sister chromatid exchange		WBC
	Micronuclei		Epithelia
	Point Mutations		
	HGPRT	Mutagenic chemicals	WBC
	Thymidine-kinase		WBC
	Oncogne activation	Chemical carcinogens (benzo[*a*]pyrene)	Tissue
	Elevated protoporphyrin	Lead	RBC
	Decreased acetylcholinesterase	Organic phosphate pesticides	Plasma

Effects biomarkers	Marker	Disease
Adverse effects (subclinical disease) markers	Altered gene expression	Liver cancer
	Serum alpha-fetoprotein	GI disease
		Fetal neural tube defect
	Carcinoembryonic antigen	GI cancers
		Other GI diseases
	Tumor-specific antigens	Various cancers
	SGOT	Myocardial infarction

abbreviations: DDE, dichlorodiphenyldichloraethylene; DDT, dichlorodiphenyetrichloroethane; WBC, white blood cell; RBC, red blood cell; HGPRT, hypoxanthine-guanine phosphoribosyl transferase; SGOT, serum glutamic-oxaloacetic transambinase; GI, gastrointestinal.[a] From (*40*).

Table 5. Examples of confirmed or postulated biomarkers for significant events in the environmental health paradigm.[a]

Exposure	Delivered dose	Biologically effective dose	Early biological effect	Altered structure or function	Clinical disease[b]	Prognostic significance
Lead	Blood lead levels	Lead level in bone marrow cells	Inhibition of *d*-aminolevulinic acid dehydratase	Accumulation of Zn protoporphyrin	Anemia	Rate of lead decrease on removal from exposure
Ethylene dioxide	Hemoglobin adducts	DNA adducts	HPRT mutation[c]	Sister chromatid exchange	Leukemia	?
Benzidine	Urinary benzidine	DNA adducts	Activated H-*ras* oncogene	DNA hyperploidy	Bladder cancer	GAG[d]
Ionizing radiation	Inhaled radionuclides	HPRT mutation	Chromosomal micronuclei	Hyperplasia	Lung cancer	Tumor antigens
Dioxin	TCDD[e] in blood	Urinary porphyrins	Hyperkeratinization of sebaceous gland	?	Chloracne	?
Fatty food	Serum cholesterol	HDL/LDL[f]	Chylomicrons in blood	Serum enzymes	Myocardial infarction	Serum enzymes
Dibromochloro-propane	DBCP in blood	?	Mean plasma FSH[g]	Sperm count	Oligospermia	Sperm motility

[a] The order of specific components in each continuum may be speculative and subject to other interpretation. [b] This component can be represented by markers but also be represented by a constellation of signs and symptoms. [c] HPRT, hypoxanthinequanine phosphoribosyl transferase. [d] GAG glycosaminoglycans. [e] TCDD, 2,3,7,8,-tetrachlordibenzo-*p*-dioxin. [f] HDL/LDL, high density lipoprotein/low density lipoprotein. [g] FSH, follicle stimulating hormone. From Schulte (*44*).

Interpreting Biomarkers for Exposure Assessment

Biologic markers can provide unequivocal evidence that exposures and uptake have occurred, and we may be able to use them as direct measurements of important dose events (e.g., internal, delivered, or target dose). Their value for exposure assessment, however, also depends on whether they can be used to reconstruct internal dose and related exposures, and on whether they aid in identifying and quantifying the relative contributions of various sources and pathways to exposure/dose.

If, for example, perfect data were available on biologically effective dose for a population of interest, identifying those individuals at the upper end of the dose distribution would be straightforward. But in the absence of relevant pharmacokinetic information, extrapolating from biologically effective dose to delivered dose and internal dose, and determining quantitatively the extent to which high (or low) internal dose is correlated with high (or low) exposure, are problematic. Thus, despite the availability of "perfect" information on target dose, it might still be necessary to use a scenario approach to estimate exposure and to determine important emission sources and exposure pathways.

Parenthetically, it is reasonable to ask why, if "perfect" data on target dose were on hand, we would need to bother estimating exposure at all. The answer lies in the realm of risk management.

Opportunities for intervention to prevent or reduce unacceptable risks occur almost exclusively in the ealier stages of the environmental health paradigm (Figures 8,9). Effective and efficient risk management strategies to protect public health typically focus on intervening at key points in the chain of events from source, to environmental concentrations, to contact between people and hazardous agents. Therefore, it is critically important from a risk management perspective to be able quantitatively to link biologic markers to exposure-related events (e.g., emissions, concentrations in environmental media, human time–activity and consumption patterns) where public or private actions, such as banning of harmful products, installation of controls, and changes in lifestyle, can reasonably be expected to produce desired results.

In summary, the utility of measuring biomarkers in human tissue for exposure assessment depends on whether we can interpret the significance of the biomarker values for exposure, dose, and causes of exposure/dose. Within this context, several important questions related to the interpretation of biomarkers need to be addressed (*43*).

How are magnitude, duration, and frequency of exposure related to the biomarker?

- How soon after exposure will the biomarker appear?
- How soon after exposure will the biomarker reach its maximum value?
- How soon after exposure will the biomarker reach its steady-state value?
- How long will the biomarker persist after exposure ends? (or alternatively, how long is its half-life?)
- What is the sensitivity and specificity of the biomarker?
- What are the intraindividual, interindividual, and between-group variabilities associated with the biomarker?

How is the marker related to the different aspects of dose?

- Is the marker a measure of internal, delivered, or biologically effective dose?
- How is the marker related to other dose events?

Is the marker specific for

- A particular agent (e.g., lead)?
- A particular source (e.g., local incinerator)?
- A particular source category (e.g., combustion sources)?
- A particular exposure setting (e.g., occupational)?

Failure to answer these and related questions can seriously limit the role of human tissue monitoring in exposure assessment.

Using Biomarkers to Improve Exposure Estimates

Although the development and application of biomarker measurements are still at a relatively early stage, there is already ample evidence showing their potential to improve estimates of exposure and dose.

An increasingly important use of human monitoring data has been as a "reality check" on indices of exposure (e.g., questionnaires, work histories). The evidence indicates that biomarkers are invaluable for letting us evaluate whether exposure indices accurately estimate and classify people according to measured dose. Needham et al. (*45*) presented case studies

Table 6. Case studies examining the relationship between exposure indices and human tissue measurements.

Study population	Environmental agent(s)	Postulated exposure pathway/route	Exposure index	Biomarker of delivered dose (body burden)	Correlation between exposure index and measured dose
Members of the U.S. Air Force directly involved in spraying Agent Orange in Vietnam	2,3,7,8,-TCDD (dioxin)	Direct contact	Scenario evaluation based on average concentration, and duration and frequency of potential exposure	Serum dioxin	None
Members of the U.S. Army (ground troops) potentially exposed to Agent Orange in Vietnam	2,3,7,8-TCDD	Skin contact and inhalation of spray; skin contact with sprayed vegetation and soil; ingestion of food and water that had been sprayed	Four indices based on potential exposure to direct spray or to areas sprayed within six days, and two indices based on self-reported data	Serum dioxin	None
Residents living near waste sites	PCBs	Skin contact with contaminated soil or water, ingestion of contaminated soil, water, or fish	Residential proximity to site	Serum PCBs	None
Residents living downstream of defunct DDT manufacturing plant	DDT, and its metabolites DDE and DDD	Ingestion of contaminated fish	Scenario evaluation based on concentrations in fish, and amount of fish eaten per week	Serum DDT, DDE, DDD	Amount of fish eaten per week significantly related to serum levels (age was the best predictor)
Workers in plants that produced chemicals contaminated with dioxin	2,3,7,8-TCDD	Occupational exposures by inhalation, ingestion, or dermal contact	Scenario evaluation based on duration of potential exposure and review of occupational records	Serum dioxin	Serum dioxin levels were significantly related to the exposure index

[a]From Needham et al. (*45*).

comparing exposure indices (e.g., a combination of environmental measurements and questionnaire data) with measurements of delivered dose (body burden). As shown in Table 6, they found that there was no correlation in three of the five cases. They concluded that when indirect measures, such as questionnaires, concentrations in environmental media, and proximity to sources, are used to estimate or classify exposures, it is important to "validate and calibrate" the exposure index against direct measurements of "internal dose" in at least a subset of the potentially exposed population.

Wallace et al. (*46*) measured levels of 25 volatile organic chemicals (VOCs) in exhaled breath, "personal" air, and indoor (residential) and outdoor air for a sample of 50 people in the Los Angeles area of California. They found that mean personal air concentrations for almost all measured VOCs were higher than indoor residential air concentrations, which, in turn, were much higher than matched outdoor values. Exhaled breath samples were significantly correlated with "personal" air measurements for the preceeding 12 hr for most VOCs. Chloroform and limonene, VOCs that did not exhibit good breath-to-air correlations, have other important routes of exposure: chloroform has dietary exposures from tap water, cold beverages, and dairy products; and limonene has dietary exposures from foods and beverages. According to their findings, VOCs in breath can provide direct evidence of exposure and dose across multiple routes, and breath measurements can make a valuable contribution to studies of VOC exposure.

Pirkle et al. (*47*) pointed out that the classic example of a biomarker that improves exposure estimates is lead in blood ("blood lead"). The accuracy and precision of blood lead measurements have improved greatly over the past 15 years, while costs have decreased. During that time, blood lead has become the standard dose metric, allowing for direct comparison of lead doses across different studies. This ability to combine multiple studies was instrumental in development of epidemiologic evidence that led to the decision by the Centers for Disease Control and Prevention (CDC) to lower the action threshold from a blood lead level of 25 μg/dl to 10 μg/dl (*47*).

The decision to phase out lead in gasoline presents a dramatic illustration of the value of blood lead as a biomarker of exposure. Prior to the decision, exposure models suggested that eliminating lead in gasoline would have a slight effect on blood lead levels (*47*). However, as shown in Figure 11, data from the second National Health and Nutrition Examination Survey (NHANES II) revealed that as lead in gasoline decreased (about 55%) from 1976 to 1980 when unleaded fuel was introduced, there was a parallel decrease (about 37%) in mean blood lead levels in the United States population (from approximately 16 μg/dl to less than 10 μg/dl) (*47,48*). These data were

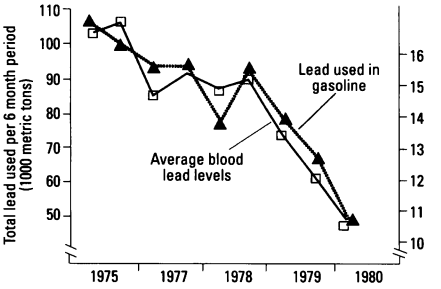

Figure 11. Observed decreases in the amount of lead used in gasoline in the United States and parallel decreases in blood lead values measured as part of NHANES II from 1976 to 1980 (*48*).

"a dominant factor" in the U.S. EPA's decision to implement a phase out of leaded gasoline (*47*).

Need for Baseline Data on Exposure and Dose

The evidence continues to mount that estimates of exposure can be improved substantially by using a combination of exposure measurements and dose measurements. Still, owing to resource constraints, relatively few studies have been conducted using this combined approach. Those that have been done are mostly small-scale, pilot-type investigations that have not employed rigorous, population-based, probability sampling techniques. Consequently, determining whether and to what extent exposure measurements and biomarker measurements are representative of people and situations beyond the original study is problematic.

With few exceptions, such as data on blood lead, there are inadequate and insufficient data to describe the exposure and dose distribution for the "general" population, as well as for those potentially at greater risk (i.e., more exposed, more susceptible, or both). It is generally not possible, therefore, to put measurements of either exposure or dose into context. That is to say, we do not have a good understanding of where the measured values fall on the local, regional, or national distribution of exposure and dose.

Such knowledge is essential if we are to make informed decisions about potential environmental hazards. This is especially true in the face of intense media pressure or public outrage. In retrospect, had the scientific information and knowledge been available to let us immediately place the monitoring data from Love Canal, New York and Times Beach, Missouri into proper perspective, both the communities and the government might have reacted differently.

There is an obvious and acute need for a national monitoring program to define the distribution of exposure and dose and to document status and trends for the United States population. Among those who have called for such a surveillance effort are the National Research Council (NRC) (*2–5*), several members of Congress (*49,50*), the Environmental Defense Fund (*51*), the U.S. EPA's Science Advisory Board (*52,53*), and a broad spectrum of the scientific community (*10,11,15–17*). The reasons that measurements of biomarkers must be an integral part of such a program have been summarized by the NRC (*4*):

- Tissue samples reflect exposures accumulated over time.
- Tissue samples reflect exposures by all routes, including some that are difficult or impossible to assess by environmental measurement (such as hand-to-mouth ingestion in young children).
- Pollutants in tissue samples have undergone the modifying effects of physiology and biologic availability.
- Some agents are more concentrated, and so more readily detectable, in tissue samples than in the environment.
- Tissue samples offer the opportunity to correlate, within a given person, the tissue concentration of toxicants with other tissue-based biologic markers or indicators of effect that might be predictive of injury or disease.

The NRC goes on to say, "All these characteristics, taken together, make tissue monitoring as an assessment tool an important adjunct to environmental monitoring that is uniquely valuable in indicating both exposures and doses that lead to potentially harmful effects" (*4*).

Changes in Nature and Scope of Risk Assessments

There are indications that the nature and scope of risk assessments are expanding in important ways, which may have significant ramifications for the role of human tissue monitoring in exposure assessment. Risks other than cancer, including adverse effects on reproduction, development, the nervous system, pulmonary and cardiovascular function, and the immune system, are becoming more important in regulatory and policy decisions. In addition to lifetime exposures, concerns increasingly focus on a wide variety of shorter term exposures: exposures from accidental or emergency releases of hazardous materials (hours or days); peak air pollution exposures during stagnant meteorological conditions (hours or days); peak waterborne exposures caused by runoff from agricultural activities (hours or days); exposures to pregnant women and fetuses during critical developmental periods (minutes or hours); and exposures of "sensitive" individuals (e.g., allergic, hypersensitive) to brief contact with environmental agents (minutes, hours, or days).

The scope of risk assessment is also broadening from a narrow focus on incremental risks associated with individual environmental agents and single exposure pathways. Now the emphasis is often on understanding "total" exposure for an individual or population from all important sources, pathways, and routes of exposure, either for a specific agent or mixture of agents. For example, instead of looking only at incremental risks related to air pollution emissions from a particular source, assessors are beginning to examine comparative and cumulative risks for the population of a defined geographic area from all important sources, via all important pathways.

These and related changes in risk assessment are being driven by a move toward more comprehensive management of environmental health risks. The magnitude and extent of environmental health problems, the associated costs of mitigation and remediation, and the need to balance the nation's budget are forcing hard societal decisions about strategic directions and how resources will be allocated among competing needs. A broad-based consensus seems to be emerging that "risk-based priority setting" is the method of choice to ensure that scarce resources are used to address the "worst" problems first. In essence, risk-based priority setting compares and ranks health risks (both cancer and noncancer), as well as other types of risks (e.g., welfare, ecologic), to establish priorities for resource allocation (*24*).

This "comparative" risk approach focuses attention on the components of "total" environmental health risk for people in a defined geographic area, such as a metropolitian center, state, region, or the entire country. To achieve its goal of identifying the worst comparative risks, risk-based priority setting requires data or informed estimates of total exposures for the population of interest. Thus, it creates an immediate need for exposure assessments that are qualitatively different from those traditionally conducted.

In the context of total exposure assessments, scenario construction alone becomes a less viable option because of the difficulties in identifying, let alone quantifying the relative contributions of all important exposure pathways. Furthermore, measurement of relevant exposure concentrations remains problematic due to the technical infeasibility of cost-effectively monitoring for all agents of interest (e.g., pesticides, metals, microorganisms, radionuclides), in all environmental media (e.g., air, beverages, food, surfaces), for all applicable settings (e.g., occupational, residential, transportational). In many instances, reconstructive exposure assessment, based on measurement of biologic markers of exposure in human tissues and excreta, is a necessary addition to exposure

assessment methodology for realistic estimation of total exposures for the population of interest.

Summary and Conclusions

Realistic assessment of health risks associated with exposures to environmental agents depends on adequate knowledge and understanding of both exposures and their associated effects. Within the risk assessment framework, exposure assessment is a formalized process, subject to explicit guidelines, that attempts to estimate the number of people exposed to specific concentrations of the agent for the period of interest, the resulting dose, and the contribution of important sources and pathways to exposure and dose. Because direct measurements of exposure and dose are scarce, and because of the narrow focus of the questions being asked, most assessments historically have been conducted by constructing exposure scenarios.

Theoretically, concentrations of environmental agents or their metabolites/derivatives measured in human tissues and excreta can be used to "reconstruct" internal dose. If this information is then combined with intake and uptake rates, it is possible to calculate associated exposures. In practice, "reconstructive exposure assessment" is seldom used because we lack appropriate pharmacokinetic information to link biomarker measurements to exposure. However, continuing scientific and technological advances in the measurement and understanding of biomarkers, as well as changes in the nature and scope of risk assessments, indicate that this approach has significant potential to improve the realism of exposure assessments.

It is important to remember, however, that direct measurements of exposure and measurements of dose are not substitutes for each other. They are complementary rather than competing methods for conducting realistic exposure assessments. The most scientifically credible risk characterizations will employ a combination of both types of evidence. Ultimately, whether measurements of biomarkers strengthen, and perhaps "revolutionize," exposure assessments depends on the extent to which we achieve a better understanding of the interrelationships among exposure pathways, exposure concentrations, and related dose.

REFERENCES

1. National Research Council. Risk assessment in the Federal Government: Managing the Process. Washington:National Academy Press, 1983.
2. National Research Council. Frontiers in Assessing Human Exposures to Environmental Toxicants. Washington:National Academy Press, 1991.
3. National Research Council. Human Exposure Assessment for Airborne Pollutants, Advances and Opportunities. Washington:National Academy Press, 1991.
4. National Research Council. Monitoring Human Tissues for Toxic Substances. Wasington:National Academy Press, 1991.
5. National Research Council. Environmental Epidemiology, Public Health and Hazardous Wastes. Vol 1. Washington:National Academy Press, 1991.
6. Sexton K, Olden K, Johnson BL. "Environmental justice": the central role of research in establishing a credible scientific basis for informed decision making. Toxicol Ind Hyg 9:685–727 (1993).
7. McMichael AJ. Setting environmental exposure standards: current concepts and controversies. Int Environ Health Res 1:2–13 (1991).
8. Hawkins NC. Conservatism in maximally exposed individual (MEI) predictive exposure assessments: A first-cut analysis. Regul Toxicol Pharmacol 14:107–117 (1991).
9. Hawkins NC, Jayjock MA, Lynch J. A rationale and framework for establishing the quality of human exposure assessments. Am Ind Hyg Assoc J 53(1):34–41 (1992).
10. Graham J, Walker KD, Berry M, Bryan EF, Callahan MA, Fan A, Finley B, Lynch J, McKone T, Ozkaynak H, Sexton K. Role of exposure databases in risk assessment. Arch Environ Health, 47,6:408–420 (1992).
11. Sexton K, Selevan SG, Wagener DK, Lybarger JA. Estimating human exposures to environmental pollutants: availability and utility of existing databases. Arch of Environ Health 47,6:398-407 (1992).
12. Whitmyre GK, Driver JH, Ginevan, ME, Tardiff, RG, Baker, SR. Human exposure assessment 1: Understanding the uncertainties. Toxicol and Environ Health, 8,5:297–320 (1992).
13. Whitmyre GK, Driver JH, Ginevan, ME, Tardiff, RG, Baker, SR. Human exposure assessment 2: quantifying and reducing the uncertainties. Toxicol and Environ Health, 8,5:321–342 (1992).
14. Wallace L. A decade of studies of human exposure: what have we learned? Risk Anal, 13, 2:135–143 (1993).
15. Burke T, Anderson H, Beach N, Colome S, Drew RT, Firestone M, Hauchman FS, Miller TO, Wagener DK, Zeise L, Tran N. Role of exposure databases in risk management. Arch of Environ Health, 47,6:421–429 (1992).
16. Goldman LR, Gomez M, Greenfield S, Hall L, Hulka BS, Kaye WE, Lybarger JA, McKenzie DH, Murphy RS, Wellington DG, Woodruff T. Use of exposure databases for status and trends analysis. Arch Environ Health 47,6:430–438 (1992).
17. Matanoski G, Selevan SG, Akland G, Bornschein RL, Dockery D, Edmonds L, Greife A, Mehlman, Shaw GM, Elliott E. Role of exposure databases in epidemiology. Arch of Environ Health, 47,6:439–446 (1992).
18. Goldstein BD. The maximally exposed individual: an inappropriate basis for public health decisionmaking. Environmental Forum;13–16 (1989).
19. McKone TE. Human exposure to chemicals from multiple media and through multiple pathways: research overview and comments. Risk Anal 11, 1:5-10 (1991).
20. McKone TE, Daniels JI. Estimating human exposure through multiple pathways from air, water, and soil. Regul Toxicol and Pharmacol 13:36-61 (1991).
21. U.S. EPA. Guidelines for Exposure Assessment; Federal Register Vol. 57, No. 104, Washington:Environmental Protection Agency, May 1992.
22. Sexton K. The role of scientific research in risk assessment and risk management decisions. Otolaryngol, Head Neck Surg 106,6:635-641 (1992).
23. Callahan MA, Bryan EF. Exposure assessment. In: Handbook of Carcinogen Testing (Milman HA, Weisburger EK, eds). Park Ridge, NJ; Noyes Publications, 651–671(1994).
24. Sexton K. An introduction to risk-based priority setting: Toward a conceptual framework for analysis. Proceedings of the Symposium on Comparative Risk Analysis and Priority Setting of Air Pollution Issues, Air and Waste Management Association, Keystone, CO (June 1993).
25. Habicht FH. Guidance on risk characterization for risk managers and risk assessors. U.S. EPA Memorandum, February 26, 1992.
26. U.S. EPA. Proposed Guidelines for Assessing Female Reproductive Risk; Notice, Part 2. Federal Register Vol. 53, No. 126. Washington:Environmental Protection Agency, June 1988.
27. U.S. EPA. Proposed Guidelines for Assessment Male

Reproductive Risk and Request for Comments, Part 3. Federal Register Vol. 53, No. 126, Washington:Environmental Protection Agency, June 1988.
28. U.S. EPA. Guidelines for Developmental Toxicity Risk Assessment; Notice, Part 5. Federal Register, vol. 56, No. 234, Environmental Protection Agency (December 1991).
29. U.S. EPA. Draft Report: Principles of Neurotoxicity Risk Assessment; Notice, Part 2. Federal Register Vol 58, No 148. Washington:Environmental Protection Agency; August 1993.
30. U.S. EPA. The Risk Assessment Guidelines of 1986. EPA/600/8–87/045. Washington:Environmental Protection Agency, 1987.
31. U.S. EPA. Workshop Report on EPA Guidelines for Carcinogen Risk Assessment: Use of Human Evidence. EPA/625/3–90/017. Washington:Environmental Protection Agency, September 1989.
32. Price PS, Sample J, Stieter R. Determination of less-than-lifetime exposures to point source emissions. Risk Anal 12,3:367–382.
33. Brown SL. Exposure assessment. In: Toxic Substances and Human Risk (Tardiff RG, Rodricks JV, Eds). New York: Plenum Press, 1987;377–390.
34. Sexton K, Ryan PB. Assessment of human exposure to air pollution: methods, measurements, and models. In: Air Pollution, the Automobile, and Public Health. (Watson AY, Bates RR, Kennedy D, eds). Washington: National Academy Press, 1988;207–238.
35. Hattis DB. The promise of molecular epidemiology for quantitative risk assessment. Risk Anal 6,2:181–193 (1986).
36. National Research Council. Biologic Markers in Pulmonary Toxicology. National Academy Press, 1989.
37. National Research Council. Biologic Markers in Reproductive toxicology. Washington:National Academy Press, 1989.
38. National Research Council. Biologic markers in immunotoxicology. Washington:National Academy Press, 1992.
39. Hulka BS, Wilcosky TC, Griffity JD, eds. Biological Markers in Epidemiology. New York:Oxford University Press, 1990.
40. Hulka BS. Overview of biological markers. In: Biological Markers in Epidemiology (Hulka BS, Wilcosky TC, Griffith JD, eds). New York: Oxford University Press, 1990;3–15.
41. Stevens DK, Bull RJ, Nauman CH, Blancato JN. Decision model for biomarkers of exposure. Regulatory Toxicology and Pharmacol 14:286–296 (1991).
42. Fowle JR, Sexton K. EPA priorities for biologic markers research in environmental health. Environ Health Perspect 98:235–241 (1992).
43. Wilcosky TC. Criteria for selecting and evaluating markers. In: Biological Markers in Epidemiology (Hulka BS, Wilcosky TC, Griffith JD, eds). New York: Oxford University Press, 1990;28–55.
44. Schulte PA. A conceptual framework for the validation and use of biologic markers. Environ Res 48:129144 (1989).
45. Needham LL, Pirkle JL, Burse VW, Patterson DG, Holler JS. Case studies of relationship between external dose and internal dose. J Exp Anal Environ Epidemiol. Suppl 1:209–221 (1992).
46. Wallace L, Nelson W, Ziegenfus R, Pellizari E, Michael L, Whitmore R, Zelon H, Hartwell T, Perritt R, Westerdahl D. The Los Angeles TEAM study: personal exposures, indoor–outdoor air concentrations, and breath concentrations of 25 volatile organic compounds. J Exp Anal Environ Epidemiol. 1,2:157-192 (1991).
47. Pirkle JL, Sampson EJ, Needham LL, Patterson DG, Ashley DL. Using biological monitoring to assess human exposure to priority toxicants. Environ Health Perspect 103.
48. Washington;EPA. Air Quality Criteria for Lead. EPA-600/8-83/028aF. Environmental Protection Agency (1986).
49. Mitchell GJ, Reid H, Lieberman JI, Metzenbaum HM. Toxic Exposure Evaluation and Monitoring Act, S.1956, Introduced into the 102d Congress but not acted on, November 13, 1991.
50. Moynihan DP. Environmental Risk Reduction Act. S.110. Introduced in the 102d Congress but not acted on, November 23, 1991.
51. Silbergeld E, Florini K. Environmental Defense Fund (EDF) Letter to Mr. R. Sussman, Deputy Administrator Designate, U.S. Environmental Protection Agency, April 22, 1993.
52. Science Advisory Board. (SAB). Future Risk: Research Strategies for the 1990s. SAB-EC-88-040. Washington: Environmental Protection Agency, September 1988.
53. Science Advisory Board. (SAB). Reducing Risk: Setting Priorities and Strategies for Environmental Protection. SAB-EC-90-021. Washington:Environmental Protection Agency, September 1990.